February 25, 2005

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Re: NAS 0; Not Product Specific
Response to FDA Request/Comment: Other
Docket No. 2004D-0484: Comments on the "Draft Guidance for Industry: Role of HIV Drug Resistance Testing on Antiretroviral Drug Development," Federal Register, Volume 69, No. 228, Pages 69374-69375, November 29, 2004

Dear Sir or Madam:

Reference is made to the notice, as published by the Food and Drug Administration in the Federal Register on November 29, 2004, to invite written comments on a new draft guidance for industry ("Role of HIV Drug Resistance Testing in Antiretroviral Drug Development") (1). The purpose of this letter is to provide comments on this new draft guidance.

GlaxoSmithKline is a research-based pharmaceutical and biotechnology company. Our company is dedicated to the discovery, development, manufacture, and distribution of medicines and vaccines that enable people to lead longer, happier, healthier, and more productive lives. GlaxoSmithKline has a long history of productive research and development of products for the treatment of HIV and other viral infections. In these efforts, we have worked constructively for almost two decades with the Division of Antiviral Drug Products and other groups within FDA, with our first approved antiretroviral drug product entering US distribution in 1987. GlaxoSmithKline holds FDA-approved New Drug Applications for Retrovir® (zidovudine) products, Epivir® (lamivudine) products, Ziagen® (abacavir sulfate) products, Agenerase® (amprenavir) products, and Lexiva® (fosamprenavir calcium) Tablets. In addition, we have ongoing activities to develop new antiretroviral drug products in a variety of classes. Our HIV clinical development and clinical virology groups have been involved in HIV resistance testing throughout the development of our approved products and maintain continued interest and expertise in these areas. In view of our longstanding work in this field and our substantial interest in the topics in this new draft guidance, we welcome this opportunity to provide comments for FDA's consideration.

In the following sections, we provide comments on the draft guidance. We have provided comments on each major section of the draft guidance. The focal point of each comment is identified by the line numbers in the draft guidance. We trust that this approach will facilitate your review and consideration of our comments.

General Comments

We welcome this draft guidance, which emphasizes the importance of resistance testing in the development of new antiretroviral agents. This guidance is generally consistent with guidances for antibacterial agents. However, the technology for antiviral resistance testing is more complex and often not standardized, therefore giving results at a higher cost (due to sample collection, shipping, and storage as well as the cost of testing) and yielding results that are more difficult to interpret (due to lack of clarity in clinical correlates) than antibacterial testing. The ability of a given assay to detect certain mutations or reduced susceptibility to an antiretroviral drug may be the result of inappropriate sampling or poor assay sensitivity. Currently, very limited FDA-approved HIV resistance assays are available for use by sponsors developing antiretroviral drugs. Since the draft guidance on the role of *in vitro* HIV drug resistance testing encourages use of genotypic and phenotypic assays, the guidance should explicitly address some of the key issues that invariably arise when a sponsor of an investigational antiretroviral drug utilizes an unapproved HIV resistance assay. We have enumerated some of these issues in comments in this letter.

We suggest that the draft guidance include a paragraph on an important guiding principle for assessment of new antiretroviral drugs, i.e., that the extent of genotypic and phenotypic resistance testing for a new antiretroviral drug product be commensurate with the value of the data obtained relative to the class of antiretroviral drug, the patient population (treatment-naïve or treatment-experienced) being evaluated, the phase of development of the drug, and the sponsor's desired labeling for the drug. Further, in general, sponsors should be encouraged to discuss the requirements and details for such testing with the Division during the periodic meetings scheduled during the course of development of a new antiretroviral drug product. We recommend that susceptibility testing to a prototypical member of each pharmacologic class of antiretroviral drug is reasonable and should be the standard expectation. Requiring baseline genotype and phenotype on all patients studied in every drug development program will have limited scientific yield, be impractical, and be cost prohibitive compared with a hypothesis-driven approach. For a new investigational antiretroviral for first-line therapy, our recommendation is to analyze genotype and phenotype at baseline and on therapy for all study patients with virologic failure and to obtain baseline genotype and phenotype on an additional representative subset of the study patients. On the other hand, for a new

antiretroviral product seeking explicit labeling for use in treatment for resistant forms of HIV, genotypic and phenotypic analyses of samples from baseline and on-treatment can be pertinent throughout development.

Although FDA does not intend for this guidance to address strategies for clinical management of patients with HIV (and resistant strains of HIV), interpretative criteria for *in vitro* susceptibility and treatment outcome need definition during drug development. Yet, in view of the limited capabilities of current assays and the clear lack of any standardized interpretative algorithms for phenotypic assays, it is substantially premature for this draft guidance and FDA to consider interpreting data from *in vitro* HIV resistance assays as "clinically relevant breakpoints." The entire hierarchy of evidence (i.e., *in vitro* data, animal models, pharmacokinetic-pharmacodynamic modeling, open-label studies, and controlled studies) must be reviewed in a New Drug Application to determine the efficacy of a new antiretroviral drug product and appropriate evidence must be summarized in prescription drug labeling (consistent with the provisions in 21 CFR 201.56). The format and content of data provided in a New Drug Application and in the labeling of an approved product should be discussed and agreed upon with the Division in advance.

I. Introduction (Pages 1-2, Lines 49-82)

Lines 51-56: FDA states on Lines 51-56 that this draft guidance is ". . . intended to assist sponsors in the clinical development of drugs for the treatment of human immunodeficiency virus (HIV) infection." GlaxoSmithKline applauds this intent and supports FDA's continued effort to provide medical/scientific information and regulatory clarification on topics that are important to fostering clinical development of new antiretroviral drugs. The Division of Antiviral Drug Products and other groups at FDA have an admirable history, for two decades, of fostering extraordinary progress in development of treatments for HIV in adult and pediatric patients. This guidance document can add to this productive history.

Lines 61-62: In our interpretation, this guidance addresses reduced susceptibility of HIV-1 that results following emergence of mutations in viral nucleic acid. However, in some situations, resistance testing of HIV-1 may yield data showing viral hypersusceptibility in the presence of one or more specific drugs, or a sequence of drugs. We recommend that the draft guidance (a) acknowledge the potential for results to show increased susceptibility of the virus to one or more antiretroviral drugs and (b) encourage sponsors to report such observations to FDA, since response to treatment may be correlated with such a finding.

Lines 70-72: The draft guidance describes how data from serial assessment of HIV genotype and phenotype can be useful in antiretroviral drug development programs. However, on Lines 70-71, FDA states that this guidance ". . . does not address any strategies for clinical management of individual patients with HIV." This seems incongruous for two reasons, i.e., (1) the regulations on prescription drug labeling call for inclusion of microbiology information within the CLINICAL PHARMACOLOGY section and (2) regulatory precedents in the labeling of some FDA-approved antiretroviral drug products provide information for clinical management of individual patients.

- The regulations on prescription drug labeling [21 CFR 201.57(b)] call for inclusion of microbiology information within the CLINICAL PHARMACOLOGY section. Usually, labeling will include information from HIV resistance testing when such methods are part of the adequate and well-controlled trials. In some cases, the results of HIV resistance testing will be sufficiently informative to merit information in labeling to guide physicians on appropriate use of the product in clinical management of individual patients with viral isolates with certain genotypic or phenotypic test results.
- There are regulatory precedents in FDA-approved labeling for information to guide clinical management of patients. For example, labeling for multiple antiretroviral drugs includes information on cross-resistance with other drugs in the same pharmacologic class; this information has a direct bearing on management of therapy-experienced patients. As a second example, labeling for many antiretroviral drugs includes a table or text describing therapeutic response among subgroups of patients with specific resistance-associated mutations at baseline; again, this information has a direct bearing on management of patients.

Statements in another part of this draft guidance (Lines 126-132) recognize the clinical relevance of resistance information, and therefore conflict with the statement on Lines 70-71. From our perspective, the statements on Lines 126-132 are reasonable and appropriate.

II. Background (Pages 2-3, Lines 85-101)

The draft guidance identifies three primary sources of information for this guidance. While we acknowledge these three important sources, we also encourage FDA to specifically acknowledge and cite the exemplary work of the *HIV Resistance Collaborative Group,* which was an important precursor activity that led to the productive meeting of the Antiviral Drugs Advisory Committee on November 2-3, 1999. The *HIV Resistance Collaborative Group* was an international, multidisciplinary effort with representatives from academic institutions, US and European health regulatory authorities, governmental clinical trial organizations (e.g., ACTG), HIV patient

community, pharmaceutical industry, and diagnostics industry. The Group included active members from three centers (CDER, CBER, and CDRH) within FDA. The *HIV Resistance Collaborative Group* was chaired by Dr. Douglas Richman (Professor of Pathology and Medicine, University of California at San Diego School of Medicine) and the Group performed its work from September 1998 through the end of 1999. Members of the Group presented most of the information for consideration at the Antiviral Drugs Advisory Committee on November 2-3, 1999, and subsequently published their results and a number of discussion papers in the first issue of Antiviral Therapy in 2000. The efforts of the *HIV Resistance Collaborative Group* are summarized in a paper by Dr. Scott Hammer (Chairperson of the Antiviral Drugs Advisory Committee in November 1999) and Dr. Louise Pedneault (GlaxoSmithKline) (2) and the Group's major analytical work was published by Dr. DeGruttola and colleagues (3). We recommend citation of references # 2 and 3 in the draft guidance document. Citation of these important contributions is appropriate, and it also serves to recognize the important roles of such academic-public-private collaborations on multidisciplinary topics, such as viral resistance.

III. HIV Resistance Testing – General (Pages 3-4, Lines 104-145)

Lines 117-119: The draft guidance states that FDA has approved only one HIV resistance assay and it does not specify this assay. The approval status of HIV resistance assays is important to the topic of this draft guidance.

To our knowledge, the Center for Biologics Evaluation and Research in FDA has permitted marketing of only two *in vitro* HIV drug resistance genotype assays (i.e., TRUGENE® HIV-1 Genotyping Kit and OpenGene® DNA Sequencing System [from Visible Genetics, Inc.] as of September 26, 2001 and ViroSeq™ HIV-1 Genotyping System [from Applied Biosystems/Celera Diagnostics] as of January 15, 2003). FDA's authorization for marketing of these two genotyping assays was in accordance with CBER's guidance governing *in vitro* HIV drug resistance genotype assays (4).

We are not aware that any of the various *in vitro* HIV phenotypic resistance assays (e.g., PhenoSense™ by ViroLogic, Antivirogram® by Virco) or other *in vitro* HIV genotypic resistance assays (e.g., GeneSeq™ by ViroLogic) have been reviewed by FDA and authorized for marketing. No phenotypic assays are approved, and only one tropism assay (PhenoSense™ Entry Assay by ViroLogic) is in investigational use, for assessment of whether an HIV-1 isolate utilizes the CCR5 or CXCR4 chemokine co-receptor.

Therefore, importantly, at this time, very limited FDA-approved HIV resistance assays are available for use by sponsors developing antiretroviral drugs. In view of this background information, and since the draft guidance on the role of *in vitro* HIV drug resistance testing encourages use of genotypic and phenotypic assays, the draft guidance should explicitly address some of the key issues that invariably arise when a sponsor of

an investigational antiretroviral drug utilizes an unapproved HIV resistance assay, including the following issues:

- Usually, for an unapproved assay, there is no regulatory application at FDA containing data and other information on the performance characteristics of the assay. Such information is usually not available to sponsors who may apply the assay in clinical studies. Although we recognize FDA's need to evaluate the quality of the assay in the context of review of a sponsor's New Drug Application (NDA), the sponsor is unable to ensure that such proprietary assay data are provided by the testing laboratory. It would be helpful if FDA can state that an NDA will not be judged deficient due to the absence of information on the performance characteristics of an unapproved assay of HIV drug resistance and if FDA could offer suggested avenues (e.g., master file, letter), other than a device marketing application, through which proprietary assay data could be provided by the testing laboratory in support of an NDA.
- For *in vitro* resistance assays of genotype, when data on assay performance is available, it would be helpful if FDA can confirm that the expectation that the sponsor (or contract testing laboratory) should provide information on assay performance, consistent with Sections III.B-D in the guidance of August 2001 (4).
- Labeling of prescription drug products should state, in the DESCRIPTION OF CLINICAL STUDIES section, the identity of any investigational or approved *in vitro* HIV resistance assay used in adequate and well controlled trials. Methodology and performance characteristics of the assay are appropriate for inclusion via citation to a REFERENCES section of labeling (as has been routine for many years for methods of assessing bacterial susceptibility to antibacterial drug products).

Lines 126-132: Note that the clinical relevance of genotypic and/or phenotypic resistance data is cited here in contrast to the statement given in Lines 70-71 above. This statement seems reasonable and appropriate to retain at Lines 126-132.

Lines 142-145: We support the objective of promoting more rational use of antiretroviral drug combinations, but we do not believe the available resistance tests alone are sufficiently advanced to support this objective. In our minds, rational selection of antiretroviral drugs for use in combination would be based, in part, on *in vitro* evidence of additive or synergistic antiviral activity and lack of antagonistic activity. In addition, early drug-drug interaction studies are essential additional data for inclusion in these considerations. Currently, we are not aware of any assay that enables reliable *in vitro* assessment of the magnitude of synergistic antiviral activity from various three or four drug combinations.

In addition, for the available assays of HIV genotype and phenotype, we are not aware of any standardized interpretative algorithms or algorithms that allow reliable interpretation of the results of one assay relative to the results of another assay. This lack

of standardized, peer-reviewed, interpretative algorithms is a barrier to FDA's objective of more rational use of antiretroviral drug combinations.

IV. Nonclinical Studies (Pages 4-7, Lines 148-311)

Lines 159-160: Regarding the conduct of *in vitro* drug combination activity studies prior to clinical use of investigational drugs, we suggest that guidance would be helpful regarding how many and what types of combinations should be assessed for antiretroviral drugs in development. From our perspective, we suggest that two practical and useful guiding principles are that (a) the sponsor of an investigational antiretroviral drug should perform *in vitro* drug combination activity studies as needed to support the specific drug-drug combinations proposed for evaluation in adequate and well-controlled clinical trials, and (b) the sponsor of an investigational antiretroviral drug should assess *in vitro* activity of its drug against HIV-1 in combination with a prototypical member of each distinct pharmacologic class of antiretroviral drugs. We understand that a guidance for nonclinical studies of antiretroviral drugs is under development and we look forward to future discussions of this topic.

Lines 178-184: The draft guidance encourages provision of the IC_{50} value to assess *in vitro* antiviral activity. Some reviewers continue to request IC_{90} values as a means to understand the concentration of the drug that inhibits a much higher proportion of the viral population. We hope this draft guidance eliminates these additional requests for IC_{90} and standardizes requests to the more precise IC_{50} value only.

Lines 183-184: A well-characterized wild-type HIV laboratory strain will be amplified more efficiently in a continuous cell line than in PBMCs. There is no advantage to growing laboratory strains in PBMCs (as there would be for clinical isolates) and, therefore, this requirement should be removed for RTIs and PIs. With respect to entry inhibitors, the choice of producer cell theoretically may make a difference but, to our knowledge, no comparative data are available.

Lines 188-194: The guidance asks for determination of antiviral activity against 50-100 well-characterized laboratory strains **and** clinical isolates. For a new investigational antiretroviral, we routinely evaluate at least 20 laboratory strains and at least 50 recombinant viruses derived from contemporary plasma of HIV-infected patients – we trust that such numbers of isolates are reasonable and consistent with FDA's intent to provide some flexibility for scientists to select a reasonable collection of laboratory and clinical isolates.

Please clarify the meaning of "real-time" isolates and the relevance of HIV-2 testing to the US population. According to a recent publication (5), the prevalence of HIV-2 as well as non-clade B viruses is < 2% in blood donors in the US.

We agree that isolates from clade B and non-clade B and from T-cell tropic and monocyte/macrophage tropic strains should be evaluated; however, further delineations of "well-characterized drug-resistance laboratory strains" and "isolates representative of the virus population where clinical trials are to be conducted" should be deleted as covered by the above specifics.

Lines 196-200: While we agree that the effect of 45-50% human serum on *in vitro* antiviral activity is important, evaluations need not be performed on multiple laboratory and clinical isolates. It is sufficient to perform such testing on a limited number of laboratory isolates, as the effect on clinical isolates can be easily extrapolated.

The use of high concentrations of human serum in tissue culture can have toxic effects on the cells. Therefore, we are inclined to include further analyses where a series of dilutions of human serum (e.g., 5%, 10%, 20%, 40%) are employed and extrapolated to 100%. In our opinion, the use of human plasma is inappropriate due to the effects of heparin or EDTA.

In addition, we acknowledge the effects of alpha-1 acid glycoprotein relative to the protein-binding effects of PIs, but we also routinely examine the protein-binding effects of human serum albumin at physiological concentrations.

Lines 202-247: Since the selection of resistant variants is difficult and time consuming, the guidance should specify exactly what the Division expects the sponsor to produce. Repeating selection experiments several times is not necessary; we recommend that the draft guidance state that the sponsor is expected to conduct *in vitro* experiments to endeavor to select drug-resistant variants under two conditions, i.e., high selective pressure and low selective pressure. Drug susceptibility should be determined both with viruses selected and with recombinant viruses containing the selected mutations, as indicated. Comments made earlier (Lines 117-119) about the lack of FDA-approved phenotype assays are relevant here, as well.

Lines 251-259: The Division should clarify whether the recombinant virus containing drug resistance mutations should be tested for susceptibility to ALL approved drugs or just a representative number of approved drugs in the same class. We recommend that susceptibility testing to a prototypical member of each pharmacologic class of antiretroviral drug is reasonable and should be the standard expectation.

The Division is aware that it can be very difficult, and impossible in some situations, for one sponsor to obtain other investigational drugs from other sponsors to use in the development of its investigational drug. Further, to our knowledge, FDA does not have the statutory or regulatory authority to compel a sponsor to provide an investigational

drug to another sponsor for *in vitro* assessment. Therefore, the requirement for testing recombinant viruses containing drug resistance-associated mutations with other investigational drugs of the same class from other sponsors should be deleted. Similarly, it is not always known which mutation(s) confers resistance to investigational drugs from other sponsors, so the requirement to test our investigational drug with viruses containing mutations resulting in resistance to other investigational drugs should be deleted.

Lines 286-288: The draft guidance asks sponsors to provide details of methodologies for *in vitro* HIV resistance assays. As stated above (Lines 117-119), such information is usually not available to a sponsor of an investigational drug who may apply the assay in clinical studies, although the contract testing laboratory may be able to supply it. It would be helpful if FDA can state that a New Drug Application will not be judged deficient due to the absence of information on the performance characteristics of an unapproved assay of HIV drug resistance.

Lines 292-298: This statement (i.e., that a New Drug Application will not be judged deficient due to the absence of information on the performance characteristics of an unapproved assay of HIV drug resistance) should also be made with respect to phenotypic assays.

Line 302: The draft guidance uses the phrase "clinically relevant breakpoints." In view of the limited capabilities of current assays and the clear lack of any standardized interpretative algorithms (as summarized above for Lines 142-145) for phenotypic assays, it is substantially premature for this draft guidance and FDA to consider interpreting data from *in vitro* HIV resistance assays as "clinically relevant breakpoints." The current standards and criteria applied to antibacterial drugs are of interest since clinically relevant breakpoints are a standard part of each New Drug Application and they are routinely quantified for inclusion in labeling. *In vitro* resistance assays for HIV are not at a similar state of standardization with regard to performance characteristics or interpretative criteria to merit similar views of clinical relevance.

V. Clinical: Use of Resistance Testing in Clinical Phases of Drug Development
(Pages 8-17, Lines 312-644)

Lines 326-328: This statement may be viewed as the Division's intent to imply that a drug with a unique resistance profile should be developed for treatment-experienced patients only. Clearly, new treatment options are also needed by therapy-naive patients. Therefore, we recommend that this draft guidance be worded in a manner to state that the Division encourages development of a new antiretroviral drug with a unique resistance

profile in appropriate treatment-experienced patients and the Division is open to concurrent clinical evaluation in therapy-naive patients.

Lines 332-334: We recognize that baseline genotype/phenotype testing is particularly useful during initial dose-ranging studies of an investigational antiretroviral with a novel resistance profile. However, we question the utility, practicality, and expense of obtaining such testing for all patients and studies. Please see our further comments regarding Lines 374-375 below.

Lines 337-346: We suggest revision of the goals of resistance testing since these goals depend, in part, on the objectives of the clinical drug development plan and such assays should not be a required part of every clinical study.

For each investigational antiretroviral drug, two goals of *in vitro* HIV resistance assays in selected clinical trials are, as follows:

1. To determine the baseline genotypic and phenotypic determinants of outcome (either virologic success or failure, or clinical success or failure) in the study.
2. To determine the association between the drug or combination of drugs of interest and study treatment-related changes in the virus (as measured using repeated assays of HIV genotype and phenotype from baseline through the time of study outcome; typically, virologic response at 48 or 96 weeks).

In addition, for an investigational antiretroviral drug where the sponsor intends to seek labeling for use in treatment-experienced patients or patients with specific drug-resistant forms of HIV, an additional goal of *ex vivo* HIV drug susceptibility assays (phenotype determinations) in selected clinical trials is to determine the susceptibility and virologic response to the drug or combination of drugs of interest in patients who have non-wild-type virus at baseline.

Lines 374-375: Requiring baseline genotype and phenotype on all patients will have very limited scientific yield, be impractical, and be cost prohibitive in many clinical studies. The yield of scientific information will be very limited in some situations, such as a controlled clinical trial in therapy-naïve patients in the US, where the prevalence of drug-resistant virus at baseline is still less than 10-15% in most areas. Requiring baseline genotype and phenotype will be impractical and cost prohibitive in many clinical studies, including certain large clinical studies, certain studies conducted in geographic settings with limited or no laboratory resources, and certain studies sponsored by governmental or other collaborative clinical trial groups. Particularly for a new investigational antiretroviral for first-line therapy, our recommendation would be to obtain baseline genotype and phenotype on all patients with subsequent virologic failure and to obtain baseline genotype and phenotype on an additional representative subset of the patients. If baseline testing is desired on all study patients, we suggest that it be limited to genotypic

testing only for RTIs and PIs, as less costly and more likely to be provide useful data. On the other hand, for a new antiretroviral product seeking explicit labeling for treatment-resistant virus, genotype and phenotype analyses of samples from baseline and on-treatment are pertinent throughout development. Overall, we suggest that the extent and type of resistance testing be discussed and agreed upon with the Division up front and be commensurate with the scientific value of the resulting data relative to study intent and nature of the drug target versus the effort and cost of such testing (see comment on Lines 477-480 below).

Lines 392-394: This sentence in the draft guidance should be revised. Sponsors can not be held responsible for monitoring *in vitro* HIV resistance during "subsequent regimens" since, in many cases, such subsequent regimens are prescribed after the clinical study period has been completed. Also, patients do not typically remain on study once loss of response to the investigational agent is determined. Longitudinal monitoring of individual patients or cohorts, outside of a controlled clinical trial, is the responsibility of the patient and his/her healthcare provider.

Lines 410-411: We consider it appropriate to provide a draft Resistance Analysis Plan to FDA for discussion at the pre-NDA meeting stage. However, we note that such a plan is not part of the format and content of an NDA per 21 CFR 314.50.

Line 426: In view of the small sample sizes in most reports of virology data, "median" change may be preferred to "mean" change. We suggest the wording "mean and/or median changes from baseline…"

Lines 434-470, Tables 1, 2A, 2B: We would suggest that analyses of virologic outcome by baseline genotype should be based on the RD=F population, as well as the as-treated population. Further, we recommend that these analyses focus on patients on an assigned treatment regimen (typically, the regimen assigned via a randomization procedure); patients who had switches in one or more of the drugs in the randomized regimen should be excluded from these analyses since it is only appropriate to explore associations between treatment-emergent changes from baseline genotype or phenotype and treatment among patients with ongoing exposure to the treatment (5).

Line 454: We note that Tables 2A and 2B provide results for the investigational agent only, rather than for all classes in the combination regimen(s). However, it should be noted that secondary mutations may also contribute to the response to the combination regimen.

Lines 477-480: Although such information could be useful, the cost of sample collection and storage, as well as the cost for multiple resistance tests, would likely be prohibitive.

We note that our current discounted assay costs are $500 for a genotype test and $950 for a phenotype test. The site charge for drawing and processing a single sample is at least $50, plus shipping costs to the testing laboratory. If such testing (both phenotype and genotype) were done at baseline and twice on-treatment (i.e., at virologic failure and subsequently) for a single study patient, the total cost would be approximately $4500. Considering that two adequate and well controlled trials for a new antiretroviral may evaluate 1600 patients, the total cost for assaying three samples from all patients would be approximately $7.2 million (the cost for assaying all baseline samples would be $2.4 million). If only patients with virologic failure are assayed (with 3 samples per patient) and assuming 15% failure, the cost would be approximately $1.1 million. These estimates do not include shipping costs. Alternatively, if samples were collected and processed (at >$50 each) and then stored but not assayed, our cost for storing a single sample is approximately $11 per tube per year; costs for shipping from the study center to a sample repository would be additional.

Line 492-501: For studies in naïve patients, baseline phenotype testing may result in mostly wild-type virus. Thus, results with patients showing decreased susceptibility could be quite biased due to the small patient numbers. We recommend that baseline susceptibility to another antiretroviral drug be evaluated only if the other antiretroviral drug is to be used as an active control in an adequate and well-controlled clinical study.

Furthermore, we question the use of "median fold change" as a breakpoint. Please note the inconsistency of this approach with that used for antibiotics as described in "Draft Guidance for Industry: Developing Antimicrobial Drugs – General Considerations for Clinical Trials" (7), and other specific FDA guidances for antibiotics. It appears that the Agency is proposing the use of the median-fold change (i.e., the 50th percentile of the baseline susceptibility frequency distribution) to determine a breakpoint. This is essentially an epidemiologic cut-off and not a clinically relevant breakpoint. In addition, please clarify the reference to "other breakpoints" that could be proposed. We reiterate (from Line 302) that, in view of the limited current assays and the clear lack of any standardized interpretative algorithms for phenotypic assays, it is substantially premature for this draft guidance and FDA to consider interpreting data from *in vitro* HIV resistance assays as "clinically relevant breakpoints." We should continue to accumulate data on the various classes of antiretroviral drugs to consider establishing such breakpoints and evaluate all available nonclinical efficacy, *in vitro* resistance data, pharmacokinetic-pharmacodynamic modeling, and clinical outcomes from open-label as well as controlled studies as pertinent to the safety and efficacy profile of a new investigational antiretroviral drug.

Lines 531-546: There are multiple challenges to following patients beyond the prospectively defined duration of evaluation in the clinical trial protocol. In addition, we reiterate that it is very difficult to follow treatment failures. Patients who have failed an

investigational drug generally prefer to enter a new trial with another new investigational antiretroviral and are reluctant to enroll in a follow-on study unless they are receiving free treatment. Also, sites are often hesitant to participate based on the effort to be expended for limited data if they are likely to have only one or two patients qualified to participate in the follow-on study. And furthermore, since subsequent therapy for treatment failures should be chosen based on resistance patterns, we question how a randomized control is feasible in the design of a rollover study.

Lines 560-562: Current pharmacogenetic analyses are conducted for hypothesis testing and require an enormous and expensive body of work for sponsors. Furthermore, we feel that FDA has not sufficiently clarified in this draft guidance how such data could be used. Therefore, we request that this point be deleted until the pharmacogenetics field advances to the point where its utility is sufficiently demonstrated and reasonably widely understood.

Line 586: Please reference our previous comments regarding the benefits of collecting baseline phenotype/genotype information on all study patients (Lines 374-375). Given the extraordinarily high cost of collecting and analyzing such samples from all patients and the relatively low prevalence of transmitted resistant HIV-1, we suggest that collecting such data may be appropriate for a small subset of study patients, but not for all treatment-naïve patients. More extensive testing is appropriate for the development of a new potent antiretroviral with a minimal cross-resistance profile in treatment-experienced patients.

Lines 591-593: For dose-ranging studies, we are not aware of any published dose-ranging studies where patients with genotypes/phenotypes were prospectively enrolled and, in fact, question whether it is feasible to find such specific patients during a study enrollment period. Alternatively, we suggest that FDA consider dose-dependent analyses of data from patients with recent virologic failure in the context of prior treatment with specific classes of antiretroviral drugs.

Lines 595-604: We maintain that resistance claims should be open to all sources of evidence, as described in FDA's May 1998 final guidance "Providing Clinical Evidence of Effectiveness for Human Drug and Biologic Products" (8). It is not appropriate for this draft guidance to define a narrower source of evidence for some antiviral drugs. The entire hierarchy of evidence must be reviewed in an application (i.e., *in vitro* data, animal models, pharmacokinetic-pharmacodynamic modeling, open-label studies, and controlled studies) and appropriate evidence must be summarized in prescription drug labeling (consistent with the provisions in regulation 21 CFR 201.56).

Lines 609-610: Again, baseline resistance testing may be useful for studies in therapy-experienced patients but it has very limited scientific yield and is not practical for studies in therapy-naïve patients.

Lines 613-615: Please consider that Phase 3 trials may study so-called "salvage" patients with no or limited treatment options, for which treatment with a new potent investigational drug with a minimal cross-resistance profile may be beneficial. In addition, in some instances, it may be of value to evaluate an investigational drug in patients with mutations that result in only minimal decreases in susceptibility.

Line 633: We question the relevance of evaluating non-clade B viruses to US registration considering their low prevalence (5). We typically test activity against non-clade B viruses *in vitro*, but not for clinical isolates.

Lines 638-642: This section should be deleted, as a draft guidance is not an appropriate mechanism for FDA to promulgate industry-wide Phase 4 commitments for an entire class of drugs.

Appendix A: Template for Submitting HIV Resistance Data (Pages 18-22, Lines 659-857)

General: We would like to point out that the obligation of the sponsor to submit viral resistance data is directly related to the nature of resistance statements sought by the sponsor in draft labeling in the future NDA. The more extensive and detailed the statements sought in draft labeling, the more evidence need be provided by the sponsor.

GSK has submitted virology data in the past and is very willing to do so in future applications, in accordance with statements sought in draft labeling. Importantly, we take this opportunity to remind FDA that it is essential that we fully agree on the format and content of such data at the pre-NDA meeting (per 21 CFR 312.47) in order to ensure that the sponsor can provide all information and analyses needed for FDA's review in the original NDA submission. The data tables provided to FDA and subsequently included in labeling should be consistent with the objectives of the drug development program. We recommend that the Division consider a variety of text descriptions as well as tabular displays and provide illustrative examples of such in this draft guidance.

Please indicate where this information should be provided for an NDA in CTD format. Per our experience with the Division, we have been instructed to include resistance assay information, as well as clinical virology reports, in Module 5, Section 5.3.5.4 "Other Studies."

Lines 684-685: Please note that some patients with documented clinical progression may have undetectable viral load and, therefore, collection of such isolates for resistance testing may not be feasible.

Lines 710-711: Both bullets include mean log change in viral load from baseline – this appears to be an error.

Line 723: Consistent with our previous comments (Lines 188-194 and Line 633), we question inclusion of clade analysis for genotypic data.

Line 772-779: Regarding the protease cleavage sites for PIs, it has been accepted for several years that the NC/p1 and p1/p6 gag cleavage sites are the most critical for polyprotein processing and are the rate-limiting sites where the key mutations arise. We see no rationale for including the p2/NC cleavage site; for us to do so would require further assay development.

Lines 854-855: Evaluation of co-receptor tropism would be pertinent only for entry inhibitors that selectively target either R5- or X4-tropic virus. Other entry inhibitors (e.g., enfuvirtide) are unlikely to have greater potential to select for virus of a particular tropism than drugs targeting other viral genes (e.g., RT, PRO, INT).

Requiring baseline tropism testing on all patients is likely to have limited scientific yield and be cost prohibitive in many clinical studies, as noted in Lines 374-375 for resistance testing. Epidemiologic studies presented to date (9, 10, 11) have shown the prevalence of X4-utilizing virus (i.e., R5X4) at baseline to be approximately 15%, with less than 4% being X4 only. We note that our current discounted assay cost is >$600 per tropism test.

It may not be possible to assay R5 and/or X4 (in terms of "relative light units") at the end of the study as the viral load may be too low. The lower validated limit of the tropism assay (PhenoSense Entry Assay) is 2000 c/mL.

Again, we thank you for this opportunity to provide comments on this important topic. This submission is provided in paper and electronic format according to the instructions provided at

http://www.accessdata.fda.gov/scripts/oc/dockets/comments/commentdocket.cfm?AGENCY=FDA.

Please contact Susan L. Watts at (919)-483-5540 or David M. Cocchetto at (919)-483-5127 for any matters regarding this submission. If you wish clarification or further discussion of our comments, we would be pleased to schedule a teleconference or meeting in follow-up. Thank you.

Sincerely,

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